Research Article / Araştırma Makalesi

Uric Acid Elevations Differ Between Equivalent Hydrochlorothiazide and Indapamide Doses

Ürik Asit Artışları Eşdeğer Hidroklorotiyazid ve İndapamid Dozları Arasında Farklılık Gösterir

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Abstract: Thiazide diuretics are among the major anti-hypertensive medications. Hydrochlorothiazide and indapamide are among the most commonly used thiazides. Common side effects include impaired renal function and electrolyte disturbances. Whether hydrochlorothiazide and indapamide cause the same amount of disturbance at equivalent doses is uncertain. Patient data from four different clinics was analyzed. Patients whose thiazide diuretic was initiated or dose escalated were included if they met the inclusion criteria. Patient characteristics, including demographics, comorbidities, medications, renal function, and electrolyte values at the initial visit and control visit, and hydrochlorothiazide or indapamide exposure per milligram, were acquired. Indapamide doses were multiplied by ten to convert into equivalent thiazide doses. Changes in renal function and electrolyte values, and renal function and electrolyte changes per equivalent thiazide exposure, were calculated. The uric acid increase and potassium decrease were different for the indapamide and hydrochlorothiazide groups. However, when these changes were analyzed per equivalent thiazide exposure, potassium was not different, but the uric acid increase was still significantly different between indapamide and hydrochlorothiazide (.05(.08) vs .03 (.08) mg/dL per equivalent mg thiazide, p = .049). This study demonstrated that indapamide's hyperuricemic effect is more profound than that of hydrochlorothiazide. Choosing hydrochlorothiazide instead of indapamide may be more appropriate in patients with higher initial uric acid levels.
Keywords: Hypertension, Uric Acid, Thiazides, Hydrochlorothiazide, Indapamide

Özet: Tiyazid diüretikleri ana anti-hipertansif ilaç gruplarındandır. Hidroklorotiyazid ve indapamid en sık kullanılan tiyazidler arasındadır. Sık izlenen yan etkileri böbrek fonksiyon ve elektrolit bozukluklarıdır. Hidroklorotiyazid ve indapamidin aynı eşdeğer dozlarında aynı miktarda bozukluğa neden olup olmadığı net değildir. Dört farklı klinikten hasta bilgileri incelendi. Tiyazid diüretik başlanan veya dozu arttırılan hastalar, dahil olma koşullarını karşılamaları durumunda çalışmaya dahil edildiler. Demografik veri, hastalıklar, ilaçlar, başlangıç ve kontrol vizitlerindeki böbrek fonksiyon ve elektrolit değerleri ile maruz kalınan hidroklorotiyazid veya indapamid dozlarından oluşan hasta özellikleri elde edildi. İndapamid dozu eşdeğer tiyazid dozuna çevrim için on ile çarpıldı. Böbrek fonksiyon ve elektrolit değerlerindeki değişimler ile eşdeğer tiyazid maruziyeti başına oluşan böbrek fonksiyon ve elektrolit değişimleri hesaplandı. İndapamid ve hidroklorotiyazid grupları arasında ürik asit artışı ve potasyum düşüşü açısından fark vardı. Bu değişimler eşdeğer tiyazid maruziyeti başına incelendiğinde potasyum düşüşü arasında fark yoktu ancak ürik asit artışı indapamid ve hidroklorotiyazid grupları arasında hala anlamlı derecede farklıydı (eşdeğer tiyazid mg'si başına .05(.08)mg/dL vs .03 (.08) mg/dL, p = .049). Bu çalışma indapamidin hiperürisemik etkisinin hydroklorotiyazidin olduğundan daha derin olduğunu göstermiştir. Başlangıç ürik asit seviyeleri daha yüksek olan hastalarda indapamid yerine hidroklorotiyazid seçilmesi daha uygun olabilir.
Anahtar Kelimeler: Hipertansiyon, Ürik Asit, Tiyazid, Hidroklorotiyazid, Indapamid

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1. Introduction

Hypertension is one of the most common cardiovascular diseases in the world (1). Anti-hypertensive medications slow or reverse hypertension-mediated organ damage; hence, strict blood pressure control is targeted in hypertensive patients (2, 3). Although many anti-hypertensive drug groups exist, only five of them are regarded as the "major drug classes" based on their efficacy and tolerability (3). Two of them are renin-angiotensin-aldosterone-system inhibitors (RAASi), namely, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). The remaining drugs include calcium channel blockers (CCB), beta blockers (Bb) and thiazide diuretics (THZ). Commonly available THZs include hydrochlorothiazide (HCTZ) and the thiazide-like diuretic indapamide. Indapamide is more potent and has a longer duration of action compared with HCTZ (4). 1 milligram (mg) of indapamide is equivalent to 10 mg of HCTZ in terms of efficacy (5).

Recent guidelines recommend the initiation of therapy with a two-drug combination for the majority of hypertensive patients (3). Of those two drugs, it is recommended that they comprise either RAASi + THZ or RAASi + CCB. The preferred side effect profile of these medications rather than their efficacy largely determines whether THZ or CCB is the better option. THZ's main side effects are metabolic and renal side effects (6). Metabolic side effects include glucose intolerance and dyslipidemia. Renal side effects include hyponatremia, hypokalemia, hyperuricemia, and hypercalcemia (6). Uric acid increases may lead to gout development and progression, as well as renal disease and cardiovascular diseases (7). Although these side effects are more pronounced with the historic HCTZ doses of 50 and 100mg, lower HCTZ doses of 12.5 and 25mg do not eliminate renal side effects completely (8, 9). Although they do not confer an absolute contraindication, these metabolic and renal side effects may cause cautious and limited use of THZs among patients with metabolic syndrome, dyslipidemia, gout, and cancer patients with bone metastasis (3). Limited and hesitant use of THZs among patients with a probable tendency for those side effects may cause inadequate hypertension control and lead to increased adverse cardiovascular outcomes.

The aim of this study was to elucidate whether there is a difference in renal function and electrolyte changes between two different THZ groups and calculate the changes in renal functions and electrolytes for a given amount of THZ medication. These data can then be embedded into clinical decision-making or machine learning algorithms in order to improve THZ utilization among high-THZ side effect-risk patients.

2. Materials and Metodhs

Design, Settings, and the Study Population

This study was designedas a post-hoc analysis of our previously published study (10). All patient data was acquired using electronic medical records (EMR). Four different clinics contributed to the study, of which one is a tertiary care university hospital general internal medicine clinic, one is a secondary care private hospital cardiology clinic, and two are secondary care state hospital general internal medicine and cardiology clinics. Outpatients admitted to these clinics between October 1st, 2020, and October 30th, 2021, were evaluated for the study.

The inclusion criteria were as follows:

- Being over 18 years old
- Having a hypertension diagnosis
- Having hydrochlorothiazide or indapamide initiated or their dose increased
- Having the control visit for renal function and electrolyte check within 4 weeks
- Having the relevant EMR data for the study

The exclusion criteria were as follows:

- Having missing or inadequate EMR data

- Being treated with mineralocorticoid receptor antagonists or loop diuretics
- Having end-stage renal or liver disease

In routine clinical practice, physicians do not routinely check renal functions and electrolytes within 4 weeks when they only initiate or dose increase thiazide medications, but they do when they initiate or dose increase RAASi. Therefore, the dose acquired via EMR represents both thiazide and RAASi initiation or dose increase. However, because RAASi other than losartan—which was used only in a few patients in the study cohort—is known not to affect uric acid levels and because there is no equivalency data for different RAASi, we did not consider which RAASi was initiated or dose increased due to the expected lack of effect on uric acid levels.

Clinical Data

The data acquired (and some calculated) for each patient were as follows:

- Demographics: age and sex
- Relevant comorbidities: diabetes mellitus, coronary artery disease, heart failure, chronic kidney disease, pulmonary diseases, active cancer, and connective tissue disorders
- Anti-hypertensive medications other than thiazides: ACEi, ARB, CCB, beta blockers, and alpha blockers
- Other common medications: insulin, oral anti-diabetics (i.e., metformin, sulphonylurea, pioglitazone, dipeptidyl peptidase-4 inhibitor (DPP4i), sodium-glucose cotransporter-2 inhibitor (SGLT-2i)), nonsteroidal anti-inflammatory drugs (NSAID), beta-2 agonists, proton pump inhibitors (PPI), and selective serotonin reuptake inhibitors (SSRI).
- Initial and control laboratory values: Urea (mg/dL), creatinine (mg/dL), estimated glomerular filtration rate (mL/min/1.73m2), uric acid (mg/dL), sodium (mEq/L), potassium (mEq/L), calcium (mg/dL), albumin (g/dL), glucose (mg/dL), low density lipoprotein (mg/dL), and triglyceride (mg/dL). These values, except for albumin, glucose, low-density lipoprotein, and triglycerides, were acquired from the EMR within 4 weeks of medication initiation or dose increase.
- Change in values: control and initial renal function and electrolyte values were subtracted to calculate the changes.
- Thiazide equivalency: 1mg of indapamide is known to be equivalent to 10 mg of hydrochlorothiazide. Therefore, all indapamide doses were multiplied by ten to make valid calculations and comparisons.
- Equivalent thiazide exposure: The thiazide medication doses to which each patient is exposed were calculated as the equivalent thiazide dose at the control visit minus the equivalent thiazide dose at the initial visit (e.g., consider a patient whose medication at the index visit was indapamide 1.5mg and it was found to be changed to hydrochlorothiazide 25 mg). First, the indapamide dose was multiplied by ten to find the equivalent thiazide dose, which is 15mg. Then, it was subtracted from the 25mg, resulting in 10mg of equivalent thiazide exposure.
- Renal function and electrolyte changes were divided by the equivalent thiazide exposures to elucidate renal function and electrolyte changes for the same amount of equivalent thiazide medication exposure.

Ethics

Each patient in the study was assigned an anonymous identification number to protect confidentiality. Processing of the data did not require informed consent, and written informed consent was not obtained due to the study's retrospective design. The study complies with the principles outlined in the Declaration of Helsinki, and this study was approved by the Hacettepe University Institutional Review Board (Project number GO22/734).

Statistics

Continuous variables were presented as median (interquartile range) and mean (±standard deviation), whereas categorical variables were presented as numbers (percentages). Pearson's chi-squared test ($\chi 2$ test) or Fisher's exact test were used for categorical variables to analyze between-group differences. The student's t-test or Mann-Whitney U test, was used for continuous variables between two groups according to their normality pattern. Statistics were provided according to the thiazide patients received. All analyses were conducted using IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL), licensed to the institution where the study was carried out. Two-sided significance testing was performed, and p-values less than 0.05 were considered significant.

3. Results

Patient Characteristics

A total of 144 patients were included in the study. Of whom, 62 were exposed to indapamide, while 82 were exposed to HCTZ. The majority of patients (66%) were female, and the mean age was 60.3 (±10.5). There was a statistically significant difference between the mean age of indapamide users (57.8±10.3) and HCTZ users (62.1±10.3). The most common comorbidities were diabetes mellitus (43.8%) and coronary artery disease (20.1%). Comorbidities were not different between indapamide users and HCTZ users ($p > .05$), except for chronic kidney disease, with zero patients in the indapamide group vs. 7 patients in the HCTZ group ($p = .01$). Regarding initial anti-hypertensive medications other than THZ, Bb was the most common (31.9%) drug, followed by CCB (27.1%) and ACEi (25.7%). Initial anti-hypertensive medications did not differ for CCB and Bb ($p > .05$) but differed between ACEi and ARB ($p < .05$). Regarding other medications, metformin (35.4%) and PPIs (20.1%) were the two most commonly used medications, and no other medications differed between the indapamide and HCTZ groups ($p > .05$). Table 1 illustrates in detail the patient characteristics for all patients and according to THZ groups.

Renal Function, Electrolytes, and Metabolic Values

Regarding initial renal functions, electrolyte values, and metabolic values, there was no difference between the indapamide and HCTZ groups ($p > .05$). Regarding the control visit's renal function and electrolyte values, there was no difference between the indapamide and HCTZ groups as well ($p > .05$).

In terms of change from initial values to control values, there was a statistically significant difference between uric acid change and potassium change. While the uric acid increase in the indapamide group was .80 (1.0), it was .47 (1.0) in the HCTZ group ($p = .014$). The potassium decrease was .2 (.5) in the indapamide group, while it was .07 (.5) in the HCTZ group ($p = .03$). Other renal function and electrolyte values did not differ between the two groups ($p > .05$). Table 2 illustrates in detail the renal function, electrolyte, and metabolic values at the initial visit, the control visit, and the change between visits, according to the THZ groups.

Equivalent Thiazide Exposure

A total of 2080mg equivalent thiazide exposure was noted in the study cohort. While indapamide initiation or dose escalation was 95.25mg in 62 patients, which is equivalent to 952.5mg of HCTZ, 1127.5mg of HCTZ initiation or dose escalation took place in 82 patients. The median equivalent thiazide exposures in the groups were used to calculate the equivalent thiazide exposure per patient. While the median equivalent thiazide exposure per patient was 12.5mg in total in the indapamide group and in the HCTZ group, there was a difference between the equivalent thiazide exposure per patient in the indapamide and HCTZ groups ($p = .04$) due to the different distribution of values (Table 3).

Renal Function and Electrolyte Changes per Equivalent Thiazide Exposure

Urea, creatinine, glomerular filtration rate, sodium, potassium, and calcium changes between the initial measurement and the control measurement per the equivalent of thiazide exposed were not different between

the indapamide and HCTZ groups (p > .05). However, the uric acid change per equivalent thiazide exposure difference was statistically significant between the two groups (p = .049). While the uric acid increased by .05 (.08) per equivalent thiazide exposure in the indapamide group, it was .03 (.08) in the HCTZ group. Table 3 illustrates in detail the equivalent thiazide exposures in total, per patient, and their associations with renal function and electrolyte changes, according to THZ groups.

Table 1. Patient characteristics according to different thiazides

	Total n = 144	**Indapamide n = 62**	**HCTZ n = 82**	**P***
Demographics				
Age	60.3 (±10.5)	57.8 (±10.3)	62.1 (±10.3)	**.01**
Female Gender	95 (66%)	41 (66.1%)	54 (65.9%)	.97
Comorbidities				
Diabetes Mellitus	63 (43.8%)	23 (36.5%)	40 (48.8%)	.16
Coronary Artery Disease	29 (20.1%)	14 (22.6%)	15 (18.3%)	.53
Heart Failure	4 (2.8%)	2 (3.2%)	2 (2.4%)	.77
Chronic Kidney Disease	7 (4.9%)	0	7 (8.5%)	**.01**
Pulmonary Disease	15 (10.4%)	4 (6.5%)	11 (13.4%)	.17
Active Cancer	3 (2.1%)	1 (1.6%)	2 (2.4%)	.73
Connective Tissue Disorder	3 (2.1%)	1 (1.6%)	2 (2.4%)	.73
Initial Major Anti-Hypertensive Medications				
ACEi	37 (25.7%)	23 (37.1%)	14 (17.1%)	**.00**
ARB	8 (18.1%)	6 (9.7%)	20 (24.4%)	**.02**
CCB	39 (27.1%)	14 (22.6%)	25 (30.5%)	.29
Beta blocker	46 (31.9%)	17 (27.4%)	29 (35.4%)	.31
Other Medications				
Insulin	19 (13.2%)	9 (14.5%)	10 (12.2%)	.80
Metformin	51 (35.4%)	19 (30.6%)	32 (39%)	.29
Sulphonylurea	13 (9%)	4 (6.5%)	9 %11%)	.34
Pioglitazone	8 (5.6%)	2 (3.2%)	6 (7.3%)	.27
DPP-4i	9 (6.3%)	2 (3.2%)	7 (8.5%)	.17
SGLT-2i	13 (9%)	6 (9.7%)	7 (8.5%)	.81
NSAID	8 (5.6%)	3 (4.8%)	5 (6.1%)	.74
Beta-2 agonists	9 (6.3%)	1 (1.6%)	8 (9.8%)	.07
Proton pump inhibitors	29 (20.1%)	9 (14.5%)	20 (24.4%)	.14
SSRI	7 (4.9%)	2 (3.2%)	5 (6.1%)	.69

ACEi: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, CCB: Calcium channel blocker, DPP4i: Dipeptidyl peptidase-4 inhibitor, HCTZ: Hydrochlorothiazide, NSAID: Nonsteroidal anti-inflammatory drug, SGLT-2i: Sodium-glucose cotransporter-2 inhibitor, SSRI: Selective serotonin reuptake inhibitor
Numbers in the brackets illustrate (± standard deviation) or (percentage %)
** P < .05 was shown in bold*

Table 2. Renal function, electrolyte, and metabolic values at the initial visit, control visit, and the change between control and initial values, according to different thiazides

Renal Function, Electrolyte, and Metabolic Values	**Total n = 144**	**Indapamide n = 62**	**HCTZ n = 82**	**P***
Initial Values				
Urea	29 (11)	30 (10)	29 (11)	.98
Creatinine	.74 (.25)	.75 (.22)	.74 (.28)	.72
Glomerular Filtration Rate	95 (20)	97 (21)	93 (19)	.60
Uric Acid	5.1 (1.4)	5.0 (1.2)	5.1 (1.6)	.35
Sodium	139 (3)	140 (2)	139 (3)	.14
Potassium	4.3 (.4)	4.3 (.6)	4.4 (.4)	.40
Calcium	9.6 (.6)	9.6 (.7)	9.6 (.6)	.98
Albumin	4.3 (.5)	4.3 (.5)	4.2 (.4)	.99
Glucose	109 (33)	105 (24)	112 (34)	.23
Low Density Lipoprotein	126 (60)	119 (65)	130 (56)	.47

Triglycerides	155 (100)	153 (99)	156 (102)	.93
Control Values				
Urea	34 (13)	35 (15)	34 (13)	.69
Creatinine	.76 (.27)	.76 (.26)	.75 (.28)	.60
Glomerular Filtration Rate	93 (24)	92 (25)	93 (24)	.94
Uric Acid	5.7 (1.5)	5.7 (1.3)	5.7 (1.6)	.53
Sodium	139 (3)	139 (2)	139 (3)	.96
Potassium	4.2 (.5)	4.1 (.6)	4.2 (.5)	.052
Calcium	9.7 (.7)	9.9 (.7)	9.6 (.6)	.24
Change in Values				
Urea	4.0 (10)	4.0 (10)	3. (9.9)	.65
Creatinine	.02 (.11)	.02 (.10)	.02 (.12)	.61
Glomerular Filtration Rate	-2 (9)	-1 (10)	-2 (10)	.85
Uric Acid	.6 (1.1)	.80 (1.0)	.47 (1.0)	**.014**
Sodium	-1.0 (3.7)	-1.7 (3.1)	-1 (3.6)	.23
Potassium	-.1 (.5)	-.2 (.5)	-.07 (.5)	**.03**
Calcium	.05 (.4)	-.05 (.4)	.1 (.4)	.47

HCTZ: Hydrochlorothiazide
Numbers in the brackets illustrate interquartile range
** P < .05 was shown in bold*

Table 3. Equivalent thiazide exposures and their associations with renal function and electrolyte changes, according to different thiazides

	Total n = 144	**Indapamide n = 62**	**HCTZ n = 82**	**P***
Equivalent thiazide exposure (mg)				
Total	2080	952.5	1127.5	
Per patient	12.5 (0)	12.5 (2.5)	12.5 (0)	**.04**
Renal function and electrolyte changes per equivalent thiazide exposure				
Urea	.24 (.72)	.24 (.72)	.24 (.71)	.77
Creatinine	.001 (.01)	.001 (.01)	.001 (.01)	.69
Glomerular Filtration Rate	-.15 (.73)	-.08 (.73)	-.16 (.74)	.89
Uric acid	.04 (.08)	.05 (.08)	.03 (.08)	**.049**
Sodium	-.08 (.28)	-.09 (.23)	-.06 (.28)	.34
Potassium	-.008 (.03)	-.008 (.04)	-.005 (.04)	.066
Calcium	.002 (.03)	-.004 (.03)	.008 (.03)	.47

HCTZ: Hydrochlorothiazide, Mg: Milligrams
Numbers in the brackets illustrate interquartile range
** P < .05 was shown in bold*

4. Discussion

This study demonstrated that indapamide causes a further increase in uric acid than does hydrochlorothiazide, per the same amount of equivalent thiazide dose. However, sodium, calcium, and potassium changes are not different between these two drugs.

Thiazide diuretics are among the first-line agents in the treatment of hypertension, both due to their high tolerability and proven ability to reduce cardiovascular morbidity and mortality (6). Thiazide diuretics can be divided into two groups: Molecules containing the benzothiadiazine ring structure are called "thiazide-type" thiazide diuretics, and hydrochlorothiazide is the prototype of this group. Those lacking the benzothiadiazine ring are called "thiazide-like" thiazide diuretics and include chlorthalidone and indapamide drugs (11). The pharmacokinetics of HCTZ, indapamide, and chlortalidone differ markedly, with the latter two having a longer half-life and higher protein binding (12). The pharmacodynamics of HCTZ, indapamide, and chlortalidone also differ markedly, especially about their pleiotropic properties (4). Regarding side effects, while hyponatremia appears similarly across agents when adjusted for potency (11), a meta-analysis illustrated that uric acid levels

slightly increase after treatment initiation with indapamide but decrease over the long term (13). Our study data included data from the first 4 weeks of drug initiation; therefore, the indapamide-induced uric acid increase could be attributed to the early uric acid measurement, but this does not explain the observed uric acid difference between equivalent hydrochlorothiazide and indapamide doses since hydrochlorothiazide would also be expected to generate a similar uric acid pattern.

Thiazide-related uric acid elevations occur due to volume contraction and competition with uric acid for renal tubular secretion. However, it does not necessarily contraindicate using a thiazide, especially if a uric acid-lowering drug such as allopurinol or SGLT-2i is also used (6, 14). On the other hand, this observation may give rise to a tendency to choose hydrochlorothiazide rather than indapamide in patients with uric acid levels at the high end.

Strengths of this study include the fact that adherence to strict inclusion and exclusion criteria caused no data to be missed. Moreover, similar patient characteristics between groups eliminated the risk of chance. Illustrating the more profound hyperuricemic effect of indapamide not only by comparing the groups directly but also by comparing them according to changes per equivalent thiazide dose eliminated the risk of comparing the effects of two unequal thiazide doses. We do acknowledge our limitations as well. First of all, this study was designed in a retrospective fashion, causing susceptibility to selection, misclassification, and recall bias. Secondly, we did not calculate the RAASi dose changes that may have caused a type B error for potassium change per equivalent thiazide exposure. Thirdly, the low number of patients in the cohort may have caused a type B error due to the lack of differences in other renal function and electrolyte changes per equivalent thiazide exposure.

In conclusion, this study showed that equivalent thiazide doses of indapamide cause a higher uric acid increase than hydrochlorothiazide. Further studies incorporating these findings into clinical decision-making and machine learning algorithms can aid clinicians in tailoring medications for different patient groups. Clinicians should opt for hydrochlorothiazide rather than indapamide when uric acid levels are of concern and thiazides are pursued.

REFERENCES

1. Brouwers S, Sudano I, Kokubo Y, Sulaica EM. Arterial hypertension. Lancet. 2021;398(10296):249-261.
2. Lønnebakken MT, Izzo R, Mancusi C, et al. Left Ventricular Hypertrophy Regression During Antihypertensive Treatment in an Outpatient Clinic (the Campania Salute Network). J Am Heart Assoc. 2017;6(3):e004152.
3. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH) [published online ahead of print, 2023 Jun 21]. J Hypertens.
4. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-head comparisons of hydrochlorothiazide with indapamide and chlorthalidone: antihypertensive and metabolic effects. Hypertension. 2015;65(5):1041-1046.
5. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56(19):1527-1534.
6. Sica DA, Carter B, Cushman W, Hamm L. Thiazide and loop diuretics. J Clin Hypertens (Greenwich). 2011;13(9):639-643.
7. Ohta Y, Kamide K, Hanada H, et al. Genetic factors associated with elevation of uric acid after treatment with thiazide-like diuretic in patients with essential hypertension. Hypertens Res. 2020;43(3):220-226.
8. Burnier M, Bakris G, Williams B. Redefining diuretics use in hypertension: why select a thiazide-like diuretic?. J Hypertens. 2019;37(8):1574-1586.
9. Lin JJ, Chang HC, Ku CT, Chen HY. Hydrochlorothiazide hypertension treatment induced metabolic effects in type 2 diabetes: a meta-analysis of parallel-design RCTs. Eur Rev Med Pharmacol Sci. 2016;20(13):2926-2934.
10. Güven AT, Özdede M, Şener YZ, et al. Evaluation of machine learning algorithms for

renin-angiotensin-aldosterone system inhibitors associated renal adverse event prediction. Eur J Intern Med. 2023;114:74-83. doi:10.1016/j.ejim.2023.05.021
11. Ernst ME, Fravel MA. Thiazide and the Thiazide-Like Diuretics: Review of Hydrochlorothiazide, Chlorthalidone, and Indapamide. Am J Hypertens. 2022;35(7):573-586.
12. Beermann B, Groschinsky-Grind M. Clinical pharmacokinetics of diuretics. Clin Pharmacokinet. 1980;5(3):221-245.
13. Weidmann P. Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies. Drug Saf. 2001;24(15):1155-1165.
14. Suijk DLS, van Baar MJB, van Bommel EJM, et al. SGLT2 Inhibition and Uric Acid Excretion in Patients with Type 2 Diabetes and Normal Kidney Function. Clin J Am Soc Nephrol. 2022;17(5):663-671.

Ethics

Ethics Committee Approval: The study was approved by Hacettepe University Non-Clinical Research Ethical Committee (Decision no:2022/12-29 Date:05.07.2022).
Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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